REMARKS

Claims 1 and 4-6 are all the claims pending in the application. Claim 1 and the specification have been amended. The specification has been amended to recite the U.S. patent counterparts to the documents cited at page 4, lines 2-14 of the specification. As such, the amendment to the specification adds no new matter.

The amendment to claim 1 is supported in the specification, such as on page 4, lines 2-14. Each of the formulas recited in claim 1 is described in U.S. Patent Nos. 5,962,493; 5,962,493; 5,998,456; and 6,288,236. Material may be incorporated by reference by way of an incorporation by reference to a U.S. Patent or U.S. patent application publication. *See* 37 C.F.R. § 1.57; MPEP § 608.01(p). In the present case, the amendments incorporate subject matter present in U.S. patents. As such, the amendment to claim 1 adds no new matter.

As a preliminary matter, Applicants respectfully submit that the Office Action includes new grounds for rejection. In this regard, withdrawal of the finality of the Office Action is respectfully requested.

I. Response to Claim Rejections - 35 U.S.C. § 112

Claims 1 and 4-6 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Referring to pages 2-3 of the Office Action, the Examiner asserts that the term "benzimidazole derivative" and "active ingredient" encompass multitudes of compounds.

Claim 1 has been amended to recite specific benzimidazole derivatives represented by the formulas recited therein. A person skilled in the art can make and use the claimed benzimidazole derivatives without undue experimentation. In this regard, claims 1 and 4-6 comply with the enablement requirement.

Additionally, claims 1 and 4-6 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Referring to pages 3-4 of the Office Action, the Examiner asserts that a person skilled in the art would not understand the metes and bounds of the phrase "benzimidazole derivative having suppressing action on foaming of macrophages."

Claim 1 no longer recites this phrase. As such, claims 1 and 4-6 are definite.

II. Response to Claim Rejections - 35 U.S.C. § 102

Claims 1-6 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by EP 0 583 665 ("EP '665").

Claim 1 presently recites that a liposome contains a benzimidazole compound and that the molar ratio of a phosphatidylcholine to a phosphatidylserine is about 1:1.

Referring to pages 4-5 of the Office Action, the Examiner asserts that the benzimidazole disclosed in EP '665 is associated with the liposome membrane under incubation conditions. As evidence, the Examiner cites U.S. Patent Nos. 6,645,522 ("US '522") and 6,348,214 ("US '214") and WO 97/25560 ("WO '560").

Page 33 of EP '665 discloses a pharmaceutical test, in which test compounds, liposomes, and 3H-Oleic acid are added to cultures of macrophages. The pharmaceutical test discloses that the test compounds and liposomes are added separately to the cultures of macrophages.

Applicants respectfully submit that EP '665 fails to describe or suggest that the liposomes thereof contain the test compounds thereof. Applicants respectfully submit that test compounds and the liposomes thereof do not associate to result in a liposome containing the test compounds thereof. A mixture of benzimidazole compounds and liposomes, by itself, does not result in the liposomes incorporating the benzimidazole.

US '522, US '214, and WO '560 fail to demonstrate that liposomes and the test compounds disclosed in EP '665 associate to provide a liposome containing the test compounds disclosed in EP '665. WO '560 discloses methods of preparing liposome products comprising biologically active amphipathic compounds in association with a liposome. *See* pages 6-7. WO '560 discloses that the method entails a) mixing a combination of lipids wherein the combination includes at least one lipid component covalently bonded to a water-soluble polymer, b) forming sterically stabilized liposomes from the combination of lipids, c) obtaining the liposomes, and d) incubating the liposomes with a biologically active amphipathic compound. *Id.* WO '560 discloses that the water-soluble polymer is preferably polyethylene glycol (PEG). *See* page 8.

Applicants respectfully submit that there are significant differences between WO '560 and EP '665, such that the method disclosed in WO '560 does not necessarily guarantee that a mixture of benzimidazole compounds and liposomes would result in the liposomes incorporating

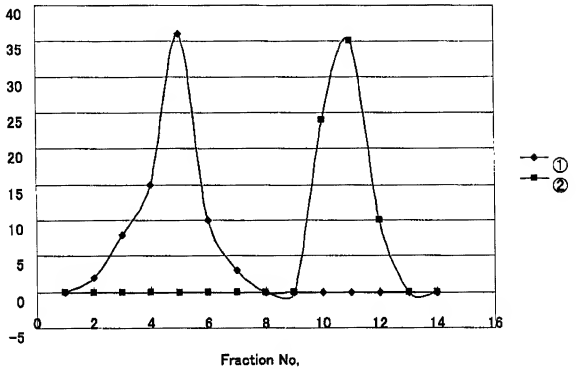
the benzimidazole compounds. For example, benzimidazole compounds are lipophilic compounds, rather than amphipathic compounds.

As evidence, Applicants have conducted a conducted an experiment comparing the liposome disclosed in WO '560 with a liposome where PC and SP = 1 ("liposome 1"). As an example of the liposome disclosed in WO '560, a liposome where PEG-DSPE : PC : PG : Chol = 0.5 : 5 : 1 : 3.5 ("liposome 2") was selected. As a benzimidazole compound, methylbenzimidazole was selected. Given the relatively low molecular weight of methylbenzimidazole, the inability of a liposome to incorporate methylbenzimidazole demonstrates that the liposome cannot incorporate the claimed benzimidazole.

Liposome 1 and liposome 2 (each 100 nmol) were suspended in 1 mL of distilled water. Solutions of ^{14}C-labeled-2-methylbenzimidazole in dimethyl sulfoxide (DMSO) were added to the suspensions to a final concentration of 1 μM. The mixtures were left to stand at room temperature for 24 hours.

Each of the mixtures was applied to a column filled with Sephadex G25 (10 mm diameter and 200 nm height). A fraction having an earlier elution time would contain liposomes, as liposomes have a higher molecular weight than 2-methylbenzimidazole. A fraction having a later elution time would consist of the labeled 2-methylbenzimidazole.

Fractions were collected. The radioactivity of each of the fractions was measured with a liquid scintillator. The results are shown in the figure below, where the vertical axis indicates the radioactivity (counts per minutes, cpm) of ^{14}C.



As shown in the figure above, the mixture containing liposome 1 showed radioactivity in fractions 1 to 8. The mixture containing liposome 2 showed radioactivity in fractions 9 to 13. These results indicate that the mixture containing liposome 1 eluted at a time significantly earlier than the elution time for the mixture containing liposome 2. In this regard, the above results indicate that liposome 1 formed liposomes incorporating the ^{14}C-labeled 2-methylbenzimidazole and that liposome was unable to form liposomes incorporating the ^{14}C-labeled 2-methylbenzimidazole.

Applicants respectfully submit that the above results establish that US '522, US '214, and WO '560 are not evidence showing that liposome and the test compounds disclosed in EP '665 associate to provide a liposome containing the test compounds disclosed in EP '665. The above experimental results demonstrate that the pharmaceutical test disclosed in EP '665 does not result in liposomes containing the test compounds thereof. As such, EP '665 fail to describe or suggest a liposome containing a benzimidazole derivative.

III. Response to Claim Rejections - 35 U.S.C. § 103

Claims 1 and 4-6 have been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over EP '665 in view of U.S. Patent No. 7,101,532 to Aikawa *et al.* ("Aikawa '532") or U.S. Patent No. 7,008,614 to Kitaguchi *et al.* ("Kitaguchi '614") or U.S. Patent No. 6,077,529 to Schmidt ("Schmidt '529") individually or in combination.

Referring to pages 5-6 of the Office Action, the Examiner contends that a person of ordinary skill in the art would have been motivated to associate benzimidazole derivatives with liposomes. For the purposes of this rejection, the Examiner concedes that EP '665 is deficient in that it fails to teach that the liposome thereof contains the test compounds thereof. The Examiner looks to Aikawa '532, Kitaguchi '614, and Schmidt '529 to make up for the deficiencies of EP '665. Aikawa '532 discloses that liposomes containing a hydrophobic iodine accumulate in vascular muscle cells and foam macrophages. *See*, col. 2, lines 50-63; *see, also*, Examples 5, 6, 8, and 9. Kitaguchi '614 also teaches that liposomes containing a hydrophobic iodine accumulate in vascular muscle cells and foam macrophages. *See*, Examples 4, 5, 7, and 8.

Schmidt '529 discloses producing asymmetrical liposomes to handle arteriosclerosis and thus extract cholesterol.

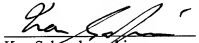
The hydrophobic iodine compounds disclosed in Aikawa '532 and Kitaguchi '614 are compounds used as contrast compounds and have no pharmacological activity. Aikawa '532 and Kitaguchi '614 fail to teach or suggest using the liposomes thereof to exhibit any pharmacological activity. EP '665 discloses suppressing the effect of macrophage-foaming reaction. In this regard, a person of ordinary skill in the art would not have been motivated to use the test compounds disclosed in EP '665 with the liposomes disclosed in Aikawa '532 and Kitaguchi '614.

Further, Applicants respectfully submit that there is no reasonable expectation of success. A person of ordinary skill in the art would have appreciated that it is much more difficult to have a liposome maintain the pharmacological activity of the compound associated therewith, than it is to have the liposome maintain the activity of an iodine compound. As described above, the hydrophobic iodine compounds disclosed in Aikawa '532 and Kitaguchi '614 are used as contrast compounds.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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